REMARKS/ARGUMENTS

Upon entry of the above claim amendments, claims 1-18 are currently pending in the present application.

Claims 14-18 are new. Support for these claims can be found in the claims as originally presented, specifically, by claims 4, 7, 8, and 9 as originally filed.

No new matter has been introduced.

Applicants expressly reserve the right to pursue any unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

Reconsideration and withdrawal of the objections and the rejections of this application in view of the amendments and remarks herewith, are respectfully requested, as the application is in condition for allowance.

Priority Claim

The Action acknowledged receipt of an English language translation of Applicants' foreign priority document, German Patent Application No. 10215942.4. The Action has also acknowledged that Applicants perfected their claim to the foreign priority. Applicants hereby thank the Examiner .

Claim Rejections under 35 U.S.C. 103(a)

Claims 1-4, 8 and 9 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Mittendorf *et al.* (U.S. Patent No. 6,262,112; hereinafter "Mittendorf") in view of Szabo et al. (J. Pharmacol. Exp. Ther., 2001, 297:819-826; hereinafter "Szabo"). The Examiner has alleged that it is obvious to a skilled artisan to modify the Mittendorf formulation with the aqueous cyclodextrin solution disclosed in Szabo to arrive at the instantly claimed formulation. Applicants respectfully traverse.

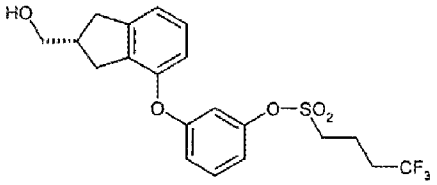
To properly determine a prima facie case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is important as

"impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." *Id.* Three criteria may be helpful in determining whether claimed subject mater is obvious under 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations. *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 (U.S. Apr. 30, 2007). With regard to the first criterion, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.3d 690 (Fed. Cir. 1990). "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render claim obvious." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002)]. The issue is whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR Int'l Co. v. Teleflex, Inc.*

The present invention is directed to an aqueous formulation of (-)-(R)-3-(2-hydroxymethylindanyl-4-oxy)phenyl 4,4,4-trifluorobutane-1-sulfonate (Compound (I)) and cyclodextrin. It was discovered by the present inventors that aqueous formulations of Compound (I) show an inhomogeneous concentration distribution, which means that infusion of the compound, especially at low active ingredient concentrations, at a constant rate over time cannot ensure administration of constant dosage levels of the compound (*see* lines 21 to 25 at page 1 of the instant application). The inventors surprisingly discovered that the addition of cyclodextrin to an aqueous formulation of Compound (I) led to more uniform concentrations of the compound (*see* lines 5 to 6 at page 2 of the application). As such, the present invention is directed to an aqueous formulation comprising Compound (I) and cyclodextrin.

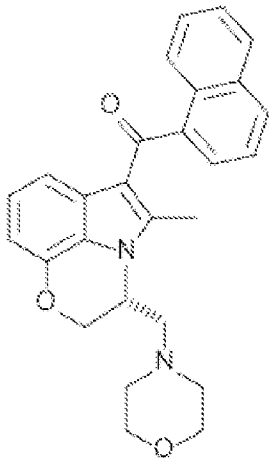
In contrast, Mittendorf does not disclose cyclodextrin, let alone any aqueous formulation comprising Compound (I) and cyclodextrin. Applicants note that Mittendorf does not appreciate the technical problem that the present inventors have faced. As such, Mittendorf does not provide any motivation or suggestion for modifying its formulations of Compound (I), let alone a specific modification leading to the presently claimed subject matters.

Applicants submit that Szabo does not disclose or teach Compound (I), let alone any aqueous formulation comprising Compound (I) and cyclodextrin. Applicants further note that Szabo does not provide any motivation or suggestion for combining cyclodextrin with Compound (I) as disclosed in Mittendorf. As also noted by the Examiner, Szabo only discloses using cyclodextrin as a co-solvent for distilled water to infuse two specific cannabinoid receptor antagonists (that is, WIN 55,212-2 and CP 55,940). Applicants have previously stated and once again submit that Compound (I) of the present application is different fundamentally in structures from WIN 55,212-2 and/or CP 55,940. To evidence the structural dissimilarities, each of Compound (I), WIN 55,212-2, and CP 55,940 is presented as follows:

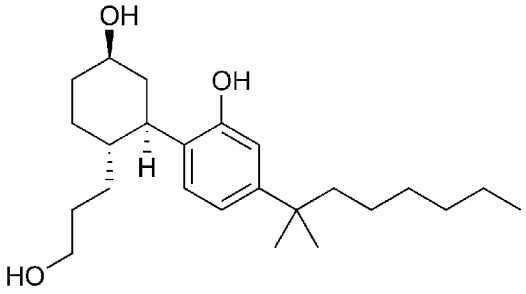


Compound (I) of the present invention

[(-)-(R)-3-(2-hydroxymethylindanyl-4-oxy)phenyl 4,4,4-trifluorobutane-1-sulfonate]

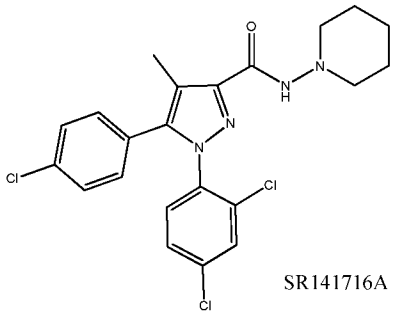


WIN 55,212-2



CP 55,940

In addition to WIN 55,212-2 and CP 55,940, Szabo discloses a third cannabinoid receptor antagonist (i.e., SR 141716A) with the structure as follows:



SR141716A

Instead of using the readily available cyclodextrin as a co-solvent, Szabo, however, teaches using 50% ethanol (v/v in saline) to dissolve SR 14716A.

Citing Liu *et al.* (Water-Insoluble Drug Formulation, p.111-140, 2000 edition, CRC Press LLC; hereinafter "Liu"), the Examiner has commented that structural relationships for determining a compound's solubility and formation of inclusion complexes with cyclodextrin are based on principles of organic chemistry, such as **size of the molecule and polarity of the molecule**. The Examiner, nevertheless, has taken a position that only the size of a guest compound's ring moiety matters in determining whether or not the compound can form inclusion complexes with cyclodextrin (*see* page 7 of the Action). The Examiner then alleges that Compound (I) has a ring size falling between those of WIN 55,212-2 and CP 55,940; thus, Compound (I) is also compatible with cyclodextrin (*see* page 7 of the Action). With respect to SR 14716A, the Examiner, without referring to any factual support or references, alleges that cyclodextrin can be used as an equivalent solvent as ethanol in infusing SR 14716A into an aqueous solution. Apparently, the Examiner herein made a cross-broad assumption that, once cyclodextrin is good for two cannabinoid receptor antagonists, cyclodextrin is good for all cannabinoid receptor antagonists regardless their structures or properties. Applicants contend that such assumption is without factual basis.

Contrary to the Examiner's assertion, Applicants submit that Liu does not teach that the formation of complexes with cyclodextrin only depends whether or not the ring size of a guest compound is compatible with the cyclodextrin cavities. Instead, Liu states expressly that "it is *very commonly* observed that the complexes form such that only certain groups or **side chains** penetrate into the carbohydrate channel" (*see* paragraph 1 at page 115 of Liu). Liu further states that "geometry certainly is not the sole factor determining the stability of a complex", and that "the

stability of a complex also depends, however, on other properties of the guess molecule, such as its **polarity**" (*see* paragraphs 1 and 5 at page 115 of Liu). Indeed, Liu indicates that, in some cases, geometry is not a major factor at all. For example, Liu reports that "β-cyclodextrin binds antazoline nearly twice as strongly as it does adiphenine," despite the fact that antazoline and adiphenine have similar molecular dimensions (*see* paragraph 5 at page 115 of Liu). Additionally, although testosterone and cortisone acetate share common structural features, β-cyclodextrin has been reported to have a definite preference for testosterone compared to cortisone acetate. *Id.*

Applicants further contend that there is no factual support for the Examiner's allegation that the ring size of Compound (I) falls between WIN 55,212-2 and CP 55,940. Even assuming that it does, the Examiner have clearly ignored other (e.g., physicochemical) properties associated with these compounds. As above discussed, the other properties can and would also determine whether or not a specific compound complexes with cyclodextrin. Applicants submit that the physicochemical properties of Compound (I) differ significantly from those of WIN 55,212-2 and CP 55,940. For example, a skilled artisan would expect that the **polarity** of Compound (I) is appreciably different from that of WIN 55,212-2 or CP 55,940. Indeed, the polarity of CP 55,940 would not be anywhere similar to that of Compound (I), due to, at least in part that CP 55,940 has three polar hydroxyl groups in its structure, while Compound (I) has only one hydroxyl group. Similarly, a skilled artisan would expect that the polarity of Compound (I) is noticeably different from that of WIN 55,212-2, as Compound (I) contains polar moieties such as hydroxyl and sulfonyl groups, while WIN 55,212-2 does not contain any substituents with comparable polarity in its structure. Accordingly, it is not possible for one skilled in the art to reasonably determine whether or not Compound (I) will behave similarly as WIN 55,212-2 and CP 55,940 in forming complexes with cyclodextrin, at least due to the significant differences in the physicochemical properties as above discussed.

Applicants submit that, rather than having reached any rule (or a reliable guidance) for a skilled artisan to predict complexation formation between any compound and cyclodextrin, Liu instead suggests that such a formation is complicated and most likely unpredictable. As discussed above, it was found unexpectedly that "β-cyclodextrin binds antazoline nearly twice as strongly as it does adiphenine" despite that a skilled artisan would expect that antazoline and adiphenine exhibit

similar affinities for β-cyclodextrin (*see* paragraph 5 at page 115 of Liu). Such a deviation from expectation in the art was also reported in Liu with respect to cortisone acetate and testosterone. *Id.*

Further, Liu demonstrates that certain chemical groups and even *different* positions of the *same* substituents may also greatly affect complex formation. For example, Liu reports that 2,6-dimethyl-4-nitrophenol forms a stable complex with cyclodextrin, and that 3,5-dimethyl-4-nitrophenol fails to form a complex at all, despite the facts that these two compounds are just a pair of isomers, which have the *same* ring structure, the *same* substituents, the *same* molecular weight, and very *similar* polarity (assuming there is any difference). Liu clearly concedes the unpredictability of the art by stating that "although some correlation exists between the binding strength and a guest molecule's structural features or other physicochemical properties, the relationship is *limited* ..." and "so far, no obvious correlation has been found between the physical or chemical properties of different families of guest molecules and complex forming ability with" cyclodextrin (*see* paragraph 4 at page 116 of Liu). In view of the foregoing discussions in Liu, a skilled artisan would agree that it is highly unpredictable for determination on whether or not a specific compound can form complexes with cyclodextrin, let alone talking about a sweeping generalization or assumption as proposed by the Examiner.

Applicants submit that it is a well-settled rule that an invention ***cannot*** be assembled by picking and choosing elements from the prior art using the claims in the present application as a "blue print." There must be some ***reason*** for the combination other than the hindsight obtained from the invention itself (*See Interconnect v. Feil,* 774 F.2d 1132 at 1143 (*Fed Cir.* 1985)). Here, the Examiner has failed to supply that reason (or any reason). In the absence of such a reason or motivation, Applicants submit that the Examiner's rejections are nothing more than the result of hindsight reconstruction of the invention based ***solely*** on Applicants' teachings. Even assuming, *arguendo,* that one were to make such a combination based on Mittendorf and Szabo, there would not be a reasonable expectation of success in the art in achieving the presently claimed subject matter due to the unpredictability nature associated with the field.

Applicants note that Szabo does not discuss any inhomogeneous distribution associated with its compounds in any formulations. That is, Szabo does not teach using cyclodextrin for the purpose to achieve more uniform concentrations of its compounds (i.e., WIN 55,212-2 and CP 55,940) in the

aqueous formulations. Indeed, Szabo only teaches using cyclodextrin to dilute the aqueous solutions of WIN 55,212-2 and CP 55,940 (*see* page 820 of Szabo). Thus, based on Szabo's disclosure, a skilled artisan would not be motivated to use cyclodextrin for improving any inhomogeneous concentration distribution of any compound, let alone with any reasonable expectation of success to achieve a more uniform concentration of Compound (I) as the present invention does.

In view of the foregoing reasons, Applicants contend that Mittendorf, either alone or in a combination with Szabo, does not establish a *prima facie* case of obviousness of the claimed subject matter, as: first, there is no suggestion or motivation furnished by either the cited references or common knowledge in the art to formulate Compound (I) with cyclodextrin (as directed by the present invention); second, the Examiner's choice of elements from the prior art to obtain the present invention is impermissible hindsight; and third, there would have been no reasonable expectation of success to a skilled artisan due to Compound (I)'s distinctiveness in structural and pharmacological properties, and the unpredictability nature of this technical field.

Therefore, reconsideration and withdrawal of the rejections under 35 U.S.C. 103 (a) on Claims 1-4, 8 and 9 is respectfully requested.

Claims 1-9 have been rejected under 35 U.S.C. §103 (a) as allegedly being unpatentable over Mittendorf in view of Szabo and Nazaki (Naunyn-Schmiedeberg's Arch. Pharmacol., 2000; hereinafter "Nakazi"). Applicants respectfully traverse.

Applicants submit that the above reasoning rebutting the rejection over Mittendorf in view of Szabo is applicable in this section of discussion, as the presently claimed subject matter is clearly patentable over Mittendorf and Szabo.

Applicants note that Nakazi only discloses additionally the use of a citrate buffer at pH 4.8 as a vehicle for cerebral infusion of WIN 55,212-2 and CP 55,940. Nakazi does not cure the deficiencies in Mittendorf and/or Szabo, as that Nakazi does not provide any motivation or suggestion for a modification leading to the present invention. Accordingly, the present invention is non-obvious over Mittendorf in view of Szabo and Nakazi. Therefore, reconsideration and withdrawal of the rejections under 35 U.S.C. 103 (a) against Claims 1-9 is respectfully requested.

Claims 1-4 and 8-10 have been rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over Mauler in view of Szabo and Yamada (U.S. Patent No. 5,807,337; hereinafter "Yamada"). Applicants hereby traverse.

Applicants submit that the above reasoning rebutting the rejection over Mittendorf in view of Szabo is also applicable in this section of discussion, as the presently claimed subject matter is clearly patentable over Mittendorf and Szabo.

Applicants submit that the disclosure of Yamada does not cure the deficiencies in Mittendorf and/or Szabo. Yamada only discloses the use of a plastic infusion apparatus for the continuous administration of therapeutic agents. Yamada does not teach or suggest the use of compound (I), let alone an aqueous formulation of Compound (I) and cyclodextrin. Further, Yamada does not furnish any motivation or suggestion that is lacked in Mittendorf and/or Szabo. Accordingly, the present invention is patentable over Mittendorf in view of Szabo and Yamada.

Therefore, reconsideration and withdrawal of the rejections under 35 U.S.C. 103 (a) on Claims 1-9 is respectfully requested.

In addition, Applicants respectfully submit that the subject matters as recited in pending claims 4, 11, 12, and 14-18 are particularly patentable over the cited references. Applicants note that none of the references teaches using from 1 to 50 g/l (that is, about 0.1% to about 5% in term of w/v) cyclodextrin in any aqueous formulation, let alone an aqueous formulation containing Compound (I). Indeed, Szabo only teaches using 19% cyclodextrin to infuse (or dissolve) WIN 55,212-2 and CP 55,940. In other words, Szabo uses cyclodextrin at a concentration at least about 4 fold higher than that recited in the instant claims. Applicants note that neither Szabo nor any other cited references suggests using cyclodextrin at a lower concentration as required by the instant claims.

As such, Applicants submit that claims 4, 11, 12, and 14-18 are patentable over all the cited art.

CONCLUSIONS

In view of the remarks made herein, the present application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. If the Examiner believes that a telephone conversation with Applicants' attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney.

It is believed that no fee is required for the submission of this paper. However, if any fee is found necessary, the Director is authorized to charge any required fee or credit any overpayment to Deposit Account No. 04-1105, Order No. 80741 (303989).

Dated: October 20, 2009

Respectfully submitted,

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